ORAL CONTRACEPTIVES AND SYSTEMIC LUPUS ERYTHEMATOSUS: WHAT SHOULD WE ADVISE TO OUR PATIENTS?

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Abstract

Oral contraceptives (OC) are the contraceptive method of choice for the majority of Western world women. Decision on giving OC to patients with Systemic Lupus Erythematosus (SLE) puts special issues and concerns. In fact, OC have been evocated as etiologic risk factors for SLE and also associated with an increased risk of flares. During periods of active disease an effective contraception is mandatory, but OC puts safety problems in this setting. On the other hand, many SLE patients will be on a low activity or remission state with much less aggressive medication for most of the time. Cumulative damage due to SLE and comorbidities such as cardiovascular disease, antiphospholipid syndrome/ antibodies also has to be considered for pregnancy and contraception decisions.

Advice on the benefits and risks of OC is an important and difficult aspect of the care of women with SLE. This advice should be done based on the best evidence and always considering our particular subject and its changing risk profile. This review will focus on OC in SLE women and particularly on current evidence on safety.

Keywords: Systemic Lupus Erythematosus; Contraception; Oral Contraceptives.

Introduction

During recent decades, generalized use of oral contraceptives (OC) by women gave them direct control of pregnancy issues and accounted to a social revolution. Since the early days, OC had the characteristic of being both the most convenient and effective non-surgical method of birth control (when taken adequately) with an acceptable safety profile. For these reasons, OC are the contraceptive method of choice for the majority of Western world women between the ages of 15 and 44 years[1].

Decision on giving OC to patients with Systemic Lupus Erythematosus (SLE) puts special issues and concerns. SLE is a chronic systemic autoimmune disease which etiology probably involves a complex interaction between environmental, infectious and hormonal factors in a genetically susceptible subject[2]. Despite it can affect any gender at any age, SLE is much more common among women and its incidence is significantly increased during reproductive years. Among the risk factors for SLE OC have been evocated as etiologic factors. During its course, SLE presents a wide range of manifestations alternating periods of exacerbation and remission. OC was also associated with an increased risk of flares with variable severity. Other clinical problems with higher occurrence among SLE patients as thrombotic events can be potentiated when OC are used.

Being SLE a disease with major expression among women, OC have been questioned for these patients over time. During periods of active disease pregnancy is contraindicated, due to risks for the patient and the baby, associated both to SLE and its treatment. For these cases, an effective contraception is mandatory but also puts special issues. On the other hand, many SLE patients will be on a low activity or remission state with much less aggressive medication for most of the time. Cumulative damage due to SLE and comorbidities such as cardiovascular disease, antiphospholipid syndrome antibodies also has to be considered for pregnancy and contraception decisions. Physicians who care of SLE women are commonly submitted to questions about these issues, not only for their patients but also from other health professionals. Advice on the benefits and risks of exogenous hormones for OC is an important and difficult aspect of the care of women with SLE. This advice should be done based on the best evidence from

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available studies and always considering our particular subject and its changing risk profile.

This review will focus on contraception in SLE women, regarding to their indications and potential risks for these particular patients.

Hormonal Contraceptives

Hormonal contraceptives prevent conception through a number of mechanisms. Ovulation is prevented by inhibition of gonadotrophin secretion via an effect on both pituitary and hypothalamic centers. Peripherally, estrogen provides endometrial stability to prevent breakthrough bleeding. Progesterone increases cervical mucus viscosity, decreases tubal peristalsis and cilial action, and diminishes the endometrial ability to support the growth of an embryo[3,4]. Progestin affect and may inhibit ovulation depending the dosage[5].

From the pharmacological point of view, hormonal methods use either a combination of estrogen and progestin or progestin only. Hormonal contraceptives can be administered through different routes: oral, transdermal, intrauterine or intravaginal[6].

The ethynilestradiol is the estrogenic component of OC. During the last years there was a progressive and significant reduction in its dose from almost 80 µg to as low as 15 µg. 17ß-estradiol has been used in transdermal patches. With the development of injections with the duration of action of 1 month, two esters of the natural hormone 17ß-estradiol (estradiol cypionate and estradiol valerate) have been used[6].

Currently, progestin employed in oral contraceptives belongs to two main chemical families: the first includes derivates from progesterone and the second derivates of 19-nortestosterone or gonane[6]. Several formula combining estrogen and progestin are available and new and old progestin can be used (drospirenone, dienogest, chlormalidone containing oral contraceptives). To avoid the side effects due to the estrogen compound, progestative only contraceptives have been developed. At present the four most often used preparations are desogestrel 75 µg, levonorgestrel 30 µg, norgestrel 30 µg and the norethisterone 350 µg/day. The newest desogestrel 75 µg presents the higher efficacy to contraception with the longer safety margin (12h) and less side effects[5,7,8]. Other progestins are used for injectable formula (depomedroxyprogesterone) and implants (levonorgestrel, etonogestrel, nestorone and nomegestrol)[5,9,10].

Why did physicians believe in a potential negative role of female hormones in SLE?

The inference that female hormones have an important role in SLE comes firstly from the highest incidence and prevalence rates of this disease among women reported over time. All studies in SLE show a female predominance. In large cohorts in Europe, USA and Latin America the majority of subjects included are women (90.8%, 88% and 90% respectively)[11-13]. When compared female to male ratios, it varies between 4.3 and 11.7. The incidence is higher among women in all ages but the difference is greater in the 15-40 years old group, with less differences in children and after 70 years of age[14-19]. The peak incidence rate for women is during puberty and during the child bearing years, suggesting an important role from sex hormones.

Experimental data with SLE models support this association. Studies conducted in mouse model SLE (NZB/NZW, MRL/1pr and BALB/c) show the role of sex hormones and its receptors in SLE onset and development, showing an increased renal disease associated with estrogen levels and that androgens are protective[20-25].

Further evidence comes from human studies reporting abnormalities in sex hormones levels. An increased level of estrogen and a low level of androgens in women with SLE were reported[26-28]. The results in male are scarcer and usually the samples are very small. Overall, significantly lower levels of testosterone and dihydrotestosterone are found in male SLE patients when compared with controls[26,29].

Furthermore, pregnancy is considered a potential trigger for SLE flare. High incidence of flares during pregnancy is reported in two prospective studies, mostly in the second trimester and post-partum[30,31]. A retrospective case control-study also shows a higher flare rate in the pregnant group (0.093 of per patient per year) than among controls (0.049 per-patient per-year). In this study, the majority of flares occurred during the second and third trimester and 8 weeks post deliver[32]. The increased level of estrogen during pregnancy could explain the risk of flare during this period and gave physicians more reasons to believe in the risk association between female hormones and SLE.

Taking in consideration all these data, hormone therapy in women with SLE remains an important concern to physicians. Observational and interventional studies were conducted over time to ascertain the role of estrogens in SLE and impro-

ved evidence necessary for giving each patient the better advice.

Oral Contraceptives and the risk of SLE

The role of exogenous estrogens as a trigger of SLE was the aim of different studies and controversial results have been published over time (Table 1).

A case control study from Sweden[33], with 85 SLE patients and 205 sex-age matched controls found no association between OC containing estrogens and SLE onset. No data related with other kind of oral contraceptives or estrogens level was analyzed. These results were similar to a previous case control study conducted by Strom et al[34] in Philadelphia. In the Carolina Lupus Study, a population based, case control study that assembled its subjects by identifying 240 SLE patients from community-based rheumatologists in South Carolina and comparing them to control subjects through driver's license records frequency-matched to cases within 5 years of age, sex and state found no correlation between OC and SLE[35]. The authors also

Table I. Evidence of risk of developing SLE associated with OC use

Author, year	Contraceptive method	Study design	Results
Strom, 1994[34]	OC unspecified	Case control study SLE: 195 Controls: 143	No association between OC´s and SLE
Sanchez Guerrero, 1997[36]	OC unspecified	Prospective cohort study NHS I (n=121 645)	Past users vs never users: RR:1.9 (95% IC: 1.1-3.3) No relation with duration of OC
Bengtsson, 2002[33]	OC containing estrogen	Case control study SLE: 85 Controls: 205	No association between OC and SLE
Cooper, 2002[35]	OC unspecified	Population-based case control study N=240 female SLE N= 320 female controls	No association between OC and SLE
Costenbader, 2007[37]	OC unspecified	Cohort study NHS I and NHSII (n=238,308) 262 SLE female	Ever use of OC: RR: 1.5 (95% IC: 1.1-2.1) Highest risk with short duration (<2y) of OC (RR: 1.9, 95%IC: 1.3-2.8) No association with kind of OC
Bernier, 2009[38]	OC	Population based nested case control-study (UK GPRD) SLE: 786 Controls: 7817	Any use of OC RR: 1.19 (95% IC: 0.98-1.45) Current use of OC RR: 1.54 (95% IC: 1.14-5.57) Risk was higher: - in current users who recently started (RR:2.52, 95% IC: 1.14-5.57) - first or second generation OC increase with dose of ethinylestradiol

NHS: Nurse Health Study; UK-GPRD: United Kingdom General Practice Registered Database
RR: Relative Risk, OR: Odds Ratio

make reference that there was no association with other hormonal contraceptives, however data related with this issue is not well clarified.

However, all previous studies were case control, based in patients self report which is associated with some limitations as bias, particularly selection and recall bias or temporal relationship difficult to establish. More recently, prospective studies using large database were conducted. Cohort studies provides some of the strongest evidence that a factor is important in a specific disease etiology with establishment of temporal relationship, minimize the bias risk and are considered the most adequate epidemiologic studies.

Prospective studies using the Nurses Health Study cohort (NHS) report an association between OC and SLE onset. Analyzing data from this cohort, past users of OC had an age and post-menopausal hormones adjusted RR of developing SLE of 1.4 (95% IC 0.9-2.1) compared with never users. On the other hand, there was no significant increased risk with duration of OC use or time since first or last use[36]**.** Furthermore, risk associated with to type of hormonal contraceptive or estrogen level was not evaluated**.** In a study conducted by Costenbader et al, using data from the same cohort, OC were associated with an increased risk of developing SLE (RR 1.5; CI 95%: 1.1-2.1) but paradoxically the risk was highest among women with shorter duration of OC use, and no association was found with type of hormones or the OC hormone potency[37].

More recently, a population-based nested case control study using the UK´s General Practice Research Database, including 786 incident cases of SLE and 7817 age matched controls, report an increased risk of SLE onset associated with OC use (RR: 1.19). The risk is greater with current use (RR: 1.54; 95% CI: 1.15-2.07), particularly among patients who had only recently started OC (RR: 2.52; 95%CI: 1.14-5.57). The risk appears to be particularly increased with current exposure to first or second generation OC (RR: 1.65; 95% CI: 1.20-2.96) and increasing with the dose of ethinylestradiol, with a RR of 2.92 for OC with 50 µg of ethinylestradiol compared to a RR of 1.42 when a dose of 30 µg is used[38].

Oral contraceptives and disease activity in SLE patients

Prescription of OC might be considered in SLE patients for several reasons. First, pregnancies and conception planned during remission have better outcomes. Secondly, most female SLE patients would appreciate to be allowed such a convenient contraceptive as OC, just like any other women. Other rationale is that patients with very active disease or those receiving potentially teratogenic medications should use an extremely reliable form of birth control. A side effect of cyclophosphamide, a common immune-suppressive therapy used in SLE patients with active disease, is infertility. Despite of actually only gonadotrophin-releasing hormone analog show some evidence in reducing the risk of ovarian failure associated with cyclophospamide[39] and no available data related with OC protective role, it is believed that oral contraceptives inhibiting ovulation can potentially mitigate infertility among cyclophosphamide users[40].

However, in SLE patients OC use was associated over time with increased risk of SLE flare. Several studies have addressed this issue (Table II).

A retrospective study conducted by Jungers et al, with 60 SLE women with renal disease, show that 43% of patients experienced an exacerbation of lupus nephritis when medicated with OC (estrogen dosage from 30µg to 50 µg of ethinylestradiol) compared to none exacerbations in control group (reogestin-only OC or non-users)[41]. Another retrospective study based on self-report of flare showed that 13% of patients referred occurrence of flare after starting OC[41]. These results were contradicted by other studies. Julkunken et al, in a retrospective study, including 85 SLE patients found no statistically significant difference in the flare rate comparing Combination OC users and non-users[43]. Studies with higher quality were later conducted to clarify this issue. The Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) is a double blind randomized placebo-controlled equivalence trial of OC therapy in pre-menopausal women. The SELENA study included 183 premenopausal women with inactive (76%) or stable active (24%) SLE, who were randomly assigned to receive either OC (triphasic ethinylestradiol 35 µg plus norethindrone at a dose of 0.5 to 1 mg for 12 cycles of 28 days) or placebo. Demographic and clinical characteristics were similar between groups. No flare increase was observed in treated patients compared to the placebo group. Discontinuation rate due to any reasons (side effects, pregnancy, voluntary or lost to follow up) was similar between groups, as well as the 12-month non adherence rate[44]. Sanchez-Guerrero et al conduc-

Table II. Evidence of OC effect on SLE activity

Author, year	Contraceptive method	Study design	Results
Jungers, 1982[40]	COC 50 µg ethynilestradiol 30 µg ethynil estradiol POC	Nonrandomized trial, non-placebo controlled SLE female with nephropathy COC 50 µg: 14 COC 30 µg: 7 POC: 11	Incidence of flare: 43% in COC groups, within 3 months of beginning OC No flare in POC group
Julkunen, 1991[42]	OC unspecified	Retrospective study	31/85 had used OC after or during SLE onset 4 (13%) noted a flare during the first six months after starting OC Incidence of flare was similar as in patients not using OC
Buyon, 1995[41]	OC unspecified	Population survey	14% (n=55) were taking OC after SLE diagnosis Only 13% (n=7) self report flare occurrence, mostly musculoskeletal
Petri et al, 2005[43]	Triphasic OC (triphasic ethinylestradiol 35 µg plus norethindrone at a dose of 0.5 to 1 mg for 12 cycles of 28 days)	RCT-double blind placebo-controlled, follow-up 12 mo 183 women with stable or inactive disease	No differences between groups in occurrence of flares of any type
Sanchez et al, 2005[44]	COC (35µg of ethinyl estradiol plus 150µg of levonorgestrel) POC(30µ Levonorgestrel) IUD (TCu 380A copper device)	RCT-single blind, non-placebo. Follow-up 12 months 162 SLE woman, ≤40 yo, with mild or stable disease	No difference among groups in mean activity, incidence of flares or time to first flare

NHS: Nurse Health Study; COC: Combined Oral Contraceptive; POC: Progestative Oral Contraceptive; IUD: Intra-Uterine Diaphragm

ted a single-blind clinical trial involving 162 women with systemic lupus erythematosus without active disease at baseline who were randomly assigned to combined OC (30 µg of ethinyl estradiol plus 150 µg of levonorgestrel), a progestin-only pill (30 µg of levonorgestrel) , or a copper intrauterine device (IUD) (TCu 380A copper device). In this study, disease activity remained mild and stable in all groups throughout the trial. There were no significant differences among the groups during the trial in global or maximum disease activity, incidence or probability of flares, or medication use. The median time to the first flare was three months in all groups[45]. In conclusion, available evidence from randomized controlled trials support the safety of low-dose combined OC in SLE patients with inactive or stable disease in regard to the risk of a SLE flare.

The first studies conducted in this area were small, not randomized, confounders not considered which limits their quality and makes it difficult to interpret the results. Discrepancies between studies could be justified by different estrogens levels with higher dosage in the early studies. Despite of better design in the recent studies, with larger samples, generalization of their results is a limitation (due to exclusion criteria) and its application in individual cases should be made carefully. As patients with active disease at baseline were excluded in both trials, no data are available about security of OC (even progestatin-only or combined pill) in patients with active disease.

Other Risks of OC in SLE patients

The estrogen component of combined OC increases hepatic production of serum globulines involved in coagulation, increases blood coaguability and the risk of thrombotic events[46]. Case control studies in the general population have shown an increased risk of deep venous thrombosis and pulmonary embolism associated to OC, ranging from 2.1 to 4.4[47], which is directly related to the dose of estrogen and the type of progesterone.

There is a high incidence of thromboembolic events (TE) in SLE patients, particularly in those with antiphospholipid antibodies (aPL)[48-52], which are common in SLE. Consequently, the decision of OC use in SLE patients should consider the presence of aPL. Other risk factors for thrombotic events recognized for general population as tobacco, venous insufficiency or other thrombophilic defects should also be considered in SLE patients.

It is actually well recognized that SLE is associated with increased cardiovascular risk not explained by traditional risk factors. SLE patients present more frequently high blood pressure. These are particular issues to be considered when a OC is prescribed to SLE patients.

Other important point is the risk of infections. SLE patients are commonly medicated with immunossupressive medications and at an increased risk of infections. The use of IUD´s is associated with an increased risk of infection in general population. No studies with SLE female patients were conducted to assess this issue, although studies including patients with IUD´s found no increased risk of infections in this group compared with OC´s[45,53]. This potential infection risk should be addressed in SLE patients.

Practical advice: Which are the best options for OC in SLE patients?

SLE presents a high incidence and prevalence among women in childbearing age, which makes the contraception an important issue to consider in these patients. Estrogens have been considered as having a deleterious effect in SLE patients, based on animal and population studies as well as in case reports. Despite case control studies have shown no increased risk of SLE onset in patients receiving OC, more recent prospective studies demonstrate an increased risk, which is related with type and dose of estrogens in OC.

Table III. Recommendations for Contraception use in SLE patients

Contraception can be considered if:

1. Absolute and relative contraindications considered for general population are not present53,54
2. Inactive or stable/moderate disease
3. No history of venous or arterial thrombosis
4. No high titer of any antiphospholipid antibody isotope
5. No lupus anticoagulant
6. No-Smoker
7. Normotensive

For combined pill, use the lowest dose of ethynilestradiol (30-35 µg)

Consideration of pill containing progestin only

Considering risk of infection if intra-uterine ring use

Prescription of OC in SLE patients should follow the same recommendations given to the general population[54,55], with particular points related with specific characteristics of this group of patients.

Although several studies have shown controversial results related to an increased risk of flare among OC users, two clinical trials show no increased rate of flare in patients with inactive or stable disease receiving OC, without difference between combined OC, progestin-only OC or IUD. No conclusions for patients with active disease are possible from these studies, and consequently OC in this group of patients should be avoided until new data appear.

Considering data for the general population, OC are associated with an increased risk of thrombotic events and its risk increases when thrombophilia exists. Despite of theoretically combination OC have higher risk of thrombotic events than Progestin-only OC, both clinical trials found no difference of thrombotic events between them. Considering conditions in the general population where OC are contraindicated in patients with higher thrombophilic risk, this is a particular issue in SLE patients, who commonly are aPL positive. So, in SLE patients aPL should be evaluated before receiving OC and if positive, combination OC should be avoided.

Despite all risks, use of OC has recognized benefits in SLE patients as birth control, and potentially may preserve ovarian function in SLE patients

receiving cyclophosphamide. For all these reasons, the possibility of OC use should be considered in SLE patients and the decision should be taken balancing benefits and risks in each individual patient.

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